Inherited Forms of Aplastic Anemia: The Inherited Bone Marrow Failure Syndromes

Blanche P. Alter

KEY CONCEPTS

- Approximately 25% of children with aplastic anemia have an underlying genetic etiology.
- Acquired and inherited aplastic anemias have critical differences in medical management.
- Hematopoietic stem cell protocols differ between acquired and inherited aplastic anemia.
- Several of the inherited aplastic anemias are associated with a high risk of leukemia and/or specific solid tumors.

Patients who present with aplastic anemia may have an acquired or an inherited etiology for their bone marrow failure. The genetic disorders must be considered and ruled out before assuming that the disorder is acquired. Many of the genetic aplastic anemias are associated with specific physical abnormalities that often lead to the correct diagnoses, and thus careful physical examination should be performed. The combination of these findings with the blood counts and bone marrow aspirates, biopsies, and cytogenetics may reveal the most likely diagnosis and identify the degree of severity of the hematopoietic problem. Mutant genes have been identified for many of the disorders, and mutation testing is often useful for final confirmation of the diagnosis, genetic counseling, prenatal diagnosis, and choice of a related, syndrome-negative, stem cell transplant donor. Details about these syndromes can be found in textbook chapters listed in Suggested Readings.

The most common of the rare inherited bone marrow failure syndromes (IBMFSs) (Table 1) associated with pancytopenia is Fanconi anemia (FA). Approximately 75% of the reported patients have characteristic birth defects, such as short stature, café au lait spots, radial ray deformities, abnormal kidneys, hearing defects, and others. Even in the absence of these features, the diagnosis of FA should be considered in any child with aplastic anemia, as well as in adults if there is any possibility of this diagnosis. Patients with dyskeratosis congenita (DC) may present with cytopenias during childhood or adolescence, whereas the pathognomonic abnormal fingernails and toenails, reticular skin pigmentation, and leukoplakia often develop during adolescence or adulthood.

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Table 239-1. Inherited Bone Marrow Failure Syndromes*

Syndrome	Age, Years	Sex	Family History	Major Characteristic Features	Hematology/Oncology	Specific Diagnostic Test	Genetics (Genes)
Fanconi anemia	0->50	M=F	Siblings	Skin pigmentation, short stature, triangular face, abnormal thumbs/radii, microcephaly, abnormal kidneys, decreased fertility	Macrocytosis, thrombocytopenia, anemia, neutropenia, hypocellular marrow MDS, leukemia, solid tumors, liver tumors	Chromosome breaks in cells cultured with DNA cross-linkers	Autosomal/X-linked recessive (>12 *FANC* genes)
Dyskeratosis congenita	0->50	M>F	Male relatives, parents, siblings	Dyskeratotic nails, Lacey reticular rash, oral leukoplakia	Macrocytosis, thrombocytopenia, anemia, neutropenia, hypocellular marrow. MDS, leukemia, solid tumors	None (short telomeres may be useful)	X-linked (*DKC1*), autosomal dominant (*TERC, TERT*), ? autosomal

							recessive
Diamond-Blackfan anemia	0->50	M=F	Parents	Short stature, abnormal thumbs	Macrocytosis, anemia, reticulocytopenia, erythroid hypoplasia in marrow MDS, leukemia, solid tumors	Elevated red cell adenosine deaminase (ADA)	Autosomal dominant (*RPS19* in 25%)
Shwachman-Diamond syndrome	0-5	M=F	Siblings	Short stature, malabsorption	Neutropenia; myeloid hypoplasia in marrow MDS, leukemia	Decreased serum trypsinogen and isoamylase	Autosomal recessive (*SBDS*)
Severe congenital neutropenia	0-1	M=F	Parents	Severe infections in infancy	Neutropenia; promyelocyte arrest in marrow MDS, leukemia	None	Autosomal dominant (*ELA-2, GFI-1*)
Thrombocytopenia and absent radii	0	M=F	Siblings	Absent radii with thumbs present	Thrombocytopenia; decreased megakaryocytes in marrow Leukemia	Arm x-ray	Autosomal recessive
Amegakaryocytic thrombocytopenia	0-5	M=F		Petechiae	Thrombocytopenia; decreased megakaryocytes in marrow Aplastic anemia, MDS, leukemia	None	Autosomal recessive (*MPL*)

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*Some patients with these syndromes have no family history, and none of the physical or hematologic features.
MDS, myelodysplastic syndrome; ?, no gene found.
From Alter BP: Bone marrow failure: A child is not just a small adult (but an adult may have a childhood disease). Hematology (Am Soc Hematol Educ Program) 2005:97-104.

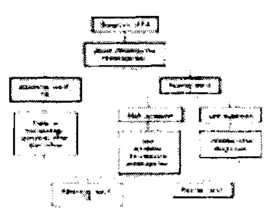

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Figure 1 Fanconi anemia (FA) diagnostic algorithm. (From Alter BP: Bone marrow failure: A child is not just a small adult [but an adult may have a childhood disease]. Hematology [Am Soc Hematol Educ Program] 2005:97-104.)

The other inherited bone marrow failure syndromes may manifest with single cytopenias. Patients with Diamond-Blackfan anemia (DBA) have pure red cell aplasia that is usually apparent in infancy, although milder cases have been identified later, including in adults. Approximately 25% have abnormal thumbs, and more than 50% have short stature. It is very unusual for DBA patients to develop full-blown aplastic anemia. Shwachman-Diamond syndrome (SDS) is characterized by malabsorption because of exocrine pancreatic insufficiency and neutropenia. The pancreatic function sometimes improves with age, and the neutropenia may become milder. However, SDS patients may also develop pancytopenia. Patients with severe congenital neutropenia (SCN) do not have a unique physical phenotype. The diagnosis depends on severe neutropenia (<200 neutrophils per mm^3) in infancy, associated with a marrow myeloid differentiation arrest at the promyelocyte/myelocyte stage. These infants may have severe pyogenic infections. Newborns with thrombocytopenia and absent radii (TAR) syndrome present with neonatal thrombocytopenia and the characteristic forearm deformities. These children usually show improved platelet counts after the first year, and there are no reports of development of aplastic anemia. In contrast, children with amegakaryocytic thrombocytopenia (amega) do not usually have birth defects, but have severely low platelet counts, and often evolve into aplastic anemia.

Figure 1 shows the algorithm for the diagnosis of FA. The gold standard is the detection of chromosome breaks in dividing cells that are cultured with a DNA cross-linker such as diepoxybutane (DEB) or mitomycin℞ C (MMC). The test is usually positive in blood T lymphocytes stimulated to divide with phytohemagglutinin. However, approximately 10% of patients with FA have hematopoietic somatic mosaicism, in which genetic reversion has occurred in differentiated or pluripotent stem cells, and the progeny of these cells are resistant to cross-link damage, as are normal cells. If the suspicion of FA remains high, skin fibroblasts can be used for the diagnostic test.

There are no diagnostic tests for the other syndromes that are as sensitive and specific as the FA test, and clinical acumen is critical. Demonstration of short telomeres in blood cells of patients with DC may be helpful but is currently a research study. Patients with DBA often have elevated red cell adenosine℞ deaminase (ADA), but this test is not useful if the patient has recently received transfusions, and there are some family members without clinical DBA who have increased ADA. Patients with SD usually have low serum trypsinogen and isoamylase levels or other evidence of exocrine pancreatic insufficiency. The diagnoses of SCN, amega, and TAR are based on clinical examinations, blood counts, and bone marrow examinations.

Table 239-2. Management Guidelines

Syndrome	When to Treat	Pharmaceutical Treatment	Transfusions	Stem Cell Transplant	Spontaneous Improvement
Fanconi Anemia	Hb <8 g/dL, or ANC <1000/mm^3, or platelets <30,000/mm^3	Androgens, usually oxymetholone℞ 2-5 mg/kg/day G-CSF, □5 mcg/kg/day	Packed red cells or platelets as needed	Bone marrow, or cord blood	Rare
Dyskeratosis congenita	Hb <8 g/dL, or ANC <1000/mm^3, or platelets <30,000/mm^3	Androgens, usually oxymetholone℞ 2-5 mg/kg/day G-CSF, □5 mcg/kg/day	Packed red cells or platelets as needed	Bone marrow, or cord blood	Rare
Diamond-Blackfan Anemia	Hb <8g/dL	Prednisone℞, 2-5 mg/kg/day	Packed red cells	Bone marrow, or cord blood	□25%
Shwachman-Diamond syndrome	ANC <1000/mm^3	G-CSF, 5-10 mcg/kg/day		Bone marrow, or cord blood	No
Severe congenital neutropenia	ANC <1000/mm^3	G-CSF, 5-10 mcg/kg/day		Bone marrow, or cord blood	No
Thrombocytopenia absent radii	Platelets <15,000/mm^3	None	Platelets as needed	Bone marrow, or cord blood	Most patients
Amegakaryocytic thrombocytopenia	Hb <8 g/dL, or ANC <1000/mm^3, or platelets <30,000/mm^3	Androgens, usually oxymetholone℞ 2-5 mg/kg/day G-CSF, □5 mcg/kg/day	Packed red cells or platelets as needed	Bone marrow, or cord blood	No

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Hb, hemoglobin; ANC, absolute neutrophil count; G-CSF, granulocyte colony-stimulating factor.
From Alter BP: Bone marrow failure: A child is not just a small adult (but an adult may have a childhood disease). Hematology (Am Soc Hematol Educ Program) 2005:97-104.

Table 239-3. Risk of Neoplasia

Syndrome	Leukemia	Solid Tumors
Fanconi anemia	Acute myeloid leukemia	Head and neck squamous cell carcinomas; gynecologic, esophageal, brain tumors
Dyskeratosis congenita	Acute myeloid leukemia	Head and neck and anogenital carcinomas
Diamond-Blackfan anemia	Acute myeloid leukemia	Osteogenic sarcomas
Shwachman-Diamond syndrome	Acute myeloid leukemia	No
Severe congenital neutropenia	Acute myeloid Leukemia	No
Thrombocytopenia and absent radii	Acute myeloid Leukemia	No
Amegakaryocytic thrombocytopenia	Acute myeloid leukemia	No

From Alter BP: Bone marrow failure: A child is not just a small adult (but an adult may have a childhood disease). Hematology (Am Soc Hematol Educ Program) 2005:97-104.

Expert Opinion on Management Issues

Research and family support groups for some of the inherited marrow syndromes have convened expert panels to develop consensus guidelines for management of the disorders. Table 2 summarizes the major indications for treatment and the types of treatment that can be considered. There is no evidence beyond the expert level, because the advice is based on case reports and consensus panels, and not on retrospective or prospective cohort studies. The FA recommendations are available online and in a book published by the Fanconi Anemia Research Fund. Results from an international consensus conference on SDS were also published recently. To date there have not been similar consensus guidelines for the other disorders, and thus physicians must rely on textbooks and on consultation with more experienced colleagues. There are several centers to which patients might be referred for diagnostic and management expertise. In particular, if stem cell transplant is being considered, it is advisable to send patients to transplant centers with expertise in the specific syndrome.

Common Pitfalls

The appropriate diagnosis is critical for management of patients with any of the inherited syndromes. Although patients with acquired aplastic anemia might respond to treatment with immunosuppressive agents, such as antithymocyte globulin and cyclosporine℞ A, patients with the inherited disorders will not respond, and precious time may be lost. If a hematopoietic stem cell transplant is chosen, the preparation that is used in acquired aplastic anemia is most likely to be toxic to patients with FA, DC, DBA, and SDS, although it may be tolerated by those with amega and perhaps TAR.

However, patients with aplasia as a consequence of FA, DC, amega, or SDS who do not have a good transplant donor may respond to treatment with androgens, granulocyte-colony stimulating factor (G-CSF), erythropoietin, or some combination. Corticosteroids are specifically effective only in DBA patients. Although in general we try to avoid transfusions of blood products unless necessary (to avoid sensitization that may jeopardize a future transplant), platelet transfusions may be critical for prevention of hemorrhage during the first year in TAR infants, who are likely to improve with time. In all cases that do require blood products, one must avoid using related donors to prevent sensitization.

Communication and Counseling

The diagnosis of the appropriate syndrome must be made as soon as possible to guide therapeutic options, and to begin to discuss prognosis and other complications that might ensue, such as leukemia or solid tumors (Table 3). Families must be offered genetic counseling, including:

- Opportunities for examination of all family members who are at risk of having the disorder in a milder form, or of being nonpenetrant carriers
- Estimates of recurrence risks in future pregnancies
- The possibilities of prenatal diagnosis and in vitro fertilization and preimplantation diagnosis

The counseling should be provided by experts who are familiar with all of the possible inheritance patterns, and who understand these rare disorders.

SUGGESTED READINGS

1. Alter BP: Inherited bone marrow failure syndromes. In Nathan DG, Orkin SH, Look AT, Ginsburg D (eds): Nathan and Oski's Hematology of Infancy and Childhood, 6th ed. Philadelphia: WB Saunders, 2003, pp 280-365. **Most recent comprehensive review of the inherited bone marrow failure syndromes.**

2. Owen J, Frohnmayer L, Eiler ME (eds): Fanconi Anemia: Standards for Clinical Care, 2nd ed. Eugene, Ore: Fanconi Anemia Research Fund, 2003. **Recommendations for diagnosis and care in FA.**

3. Fanconi Anemia Research Fund: Available online at Click here **Website of the Fanconi Anemia Research Fund, with links to their published books and newsletters.**

4. Rothbaum R, Perrault J, Vlachos A, et al: Shwachman-Diamond syndrome: Report from an international conference. J Pediatr 141:266-270, 2002. **Recommendations for diagnosis and care in SDS.** Medline Similar articles Full article

5. Young NS, Alter BP: Aplastic Anemia: Acquired and Inherited. Philadelphia: WB Saunders, 1994. **Comprehensive review of acquired and inherited aplastic anemias.**

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Reyes, Jose (NIH/NCI) [E]

From: Nicole Dupree [NicoleDupree@westat.com]
Sent: Thursday, June 01, 2006 4:23 PM
To: Reyes, Jose (NIH/NCI) [E]
Cc: Barbara Hayden
Subject: Certificate of Appreciation
Signed By: nicoledupree@westat.com

Hi Jose,

I need a Certificate of Appreciation for **Janet Schott**.

Thanks,

Nicole

Nicole Dupree
Research Assistant
Clinical Genetics Branch
NCI/ Westat
301-881-1461
nicoledupree@westat.com